ORIGINAL ARTICLE

# Calcium and Aspirin Supplementation for Prevention of Pre-eclampsia in Moderate to High-Risk Pregnancy: A Randomized Controlled Trial

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**Background**: Pregnancy-induced hypertension is one of the major causes of both maternal and fetal death. Calcium can be prescribed to prevent the development of pre-eclampsia among the population with low calcium intake. However, there are only a few research studies on the effect of calcium alone, the impact of calcium co-administrated with other medications, and the timing of prescription during pregnancy.

**Materials and Methods**: The authors conducted a randomized, single-blind, controlled trial to evaluate the efficacy of high-dose calcium carbonate ($CaCO_3$) co-administrate with aspirin in women with moderate to high risk of developing pre-eclampsia in reducing the incidence of pre-eclampsia. All pregnant women at 12 to 28 weeks of gestation having a moderate to high risk of developing pre-eclampsia were randomly assigned to receive aspirin with $CaCO_3$ (3,750 mg/day), or aspirin with standard dose calcium carbonate (1,250 mg/day) until delivery or developed pre-eclampsia.

**Results**: One hundred thirty women underwent randomization with 64 women in the $CaCO_3$ group and 66 women in the standard dose group. The incidence of pre-eclampsia was six cases in the high-dose group and eight cases in the controlled group (OR 0.8, 95% CI 0.3 to 2.6). The percentage of participants having adverse events related to high-dose and standard dose calcium carbonate did not differ significantly between the groups.

**Conclusion**: The use of $CaCO_3$ at 3,750 mg/day, co-administrate with low-dose aspirin of 81 mg/day, starting at 12 to 28 weeks of gestation, resulted in a non-significantly difference in the incidence of pre-eclampsia with severe features.

**Keywords**: Calcium carbonate; Pre-eclampsia; Prevention

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Pregnancy-induced hypertension (PIH) is one of the major causes of both maternal and fetal death. Nearly one-tenth of all maternal mortality in Africa and Asia is associated with hypertensive disorders of pregnancy[1]. Aspirin and calcium supplementations are one of the interventions that can prevent pre-eclampsia and related problems.

The American College of Obstetricians and Gynecologists (ACOG) recommended 81 mg/day of aspirin prophylaxis initiated between 12 weeks and 28 weeks of gestation and continued daily until delivery in patients at high risk of pre-eclampsia. Furthermore, a low-dose aspirin for pregnant patients with more than one moderate-risk factor should be considered[2]. High-dose calcium carbonate ($CaCO_3$) supplementation with 1.5 to 2.0 g of elemental calcium daily is also recommended from 20 weeks of gestation until delivery in populations where calcium intake is low for the prevention of pre-eclampsia, particularly among those at higher risk of developing PIH[3]. High risk of developing pre-eclampsia is defined in the World Health Organization (WHO) guideline as having one or more of the following risk factors, history of pre-eclampsia, diabetes, pre-existing hypertension, obesity, autoimmune disease, nulliparity, adolescent pregnancy, renal disorders, advanced maternal age, and conditions leading to hyperplacentation and large placentas[3]. The risk classification is different between ACOG and WHO guidelines, in which ACOG classifies into three tiers, but two in the WHO guideline. Moreover, the risk definitions are also different.

There are a few trial studies on $CaCO_3$ supplementation co-administrate with aspirin for pre-

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eclampsia prevention. The 3-arm prospective randomized clinical trial (RCT) was conducted in Trinidad to evaluate the effect of 1,200 mg of elemental calcium compared with 600 mg of elemental calcium plus 80 mg of aspirin compared with 80 mg of aspirin alone in the incidence of pre-eclampsia in 510 women[4]. They found that the incidence of pre-eclampsia was lowest in the 1,200 mg of calcium group compared to calcium plus aspirin and aspirin alone group at 1.2%, 2.4%, and 8.0%, respectively ($p<0.01$ in calcium versus aspirin, and $p<0.05$ in calcium versus calcium/aspirin). The present study recruited all primigravida and multigravidas with an obstetrics history of pre-eclampsia. Another double-blind, placebo-controlled RCT in Brazil compared the incidence of superimposed pre-eclampsia in 49 women with pre-existing hypertension and uterine artery doppler abnormality at 20 to 27 weeks of gestation versus placebo[5]. The difference in the incidence of superimposed pre-eclampsia was not observed in the present study ($p=0.112$).

In the safety aspect, most systematic reviews of randomized controlled trials have found low-dose aspirin during pregnancy is not associated with hemorrhagic complication. No increase in hemorrhagic complications associated with low-dose aspirin during pregnancy[6-8]. The use of low-dose aspirin during pregnancy is not associated with hemorrhagic complications, placental abruption, postpartum hemorrhage, or mean blood loss[7]. There is also no safety concern on the risk of congenital anomalies[6-8] and adverse fetal or neonatal effects in the RCT of 1,228 women of which 615 participants received low-dose aspirin starting before pregnancy and continuing throughout pregnancy[9]. Low-dose aspirin use during the third trimester is also not associated with ductal closure[10,11]. The RCT involving 30,000 women who received low-dose aspirin versus placebo found no increase in perinatal deaths from persistent pulmonary hypertension[6,7,12].

Calcium can be prescribed to prevent the development of pre-eclampsia among the population with low calcium diet[3]. However, there is no trial testing the effect of high-dose $CaCO_3$ plus low-dose aspirin for the prevention of pre-eclampsia in women with moderate- to high-risk of developing pre-eclampsia defined by the current standard guidelines. There is also no evidence testing the timing of high-dose $CaCO_3$ initiation[3].

The authors hypothesized that high-dose $CaCO_3$ co-administrating with low-dose aspirin could reduce the incidence in patients at risk of pre-eclampsia. The risk of pre-eclampsia is defined as recommended in ACOG and USPSTF.

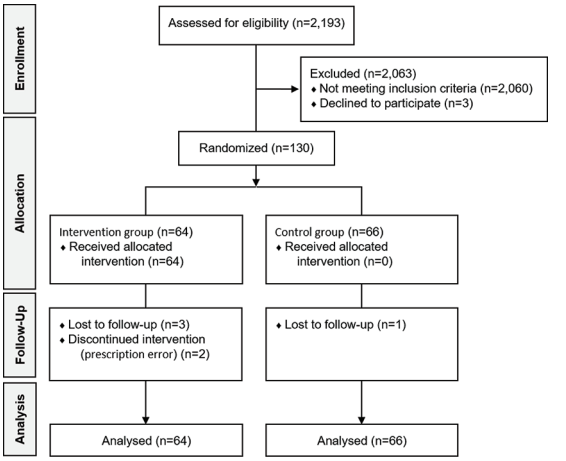


**Figure 1.** Flow diagram following the CONSORT guidelines.

## Materials and Methods

The authors conducted a single-blind, randomized controlled trial at the antenatal clinic in Chonburi Hospital, the largest tertiary hospital in the eastern region of Thailand between April 2021 and November 2022. The present study was registered in the Thai Clinical Trial Registry (TCTR20221001001). The study protocol was approved by the Institutional Review Boards (number), and all the participants provided written informed consents before randomization.

### Study subjects

All pregnant women who visited the antenatal clinic at less than 28 weeks of gestation were screened with a validated question form and verified with the physician. Those who have one or more high-risk or two or more moderate risks of developing pre-eclampsia were enrolled in the present study, and blood tests were drawn for serum calcium and albumin level. High risk of developing pre-eclampsia was defined as a pregnant woman with multifetal gestation, pre-existing hypertension, renal disorders, type 1 or type 2 diabetes, autoimmune disease such as systemic lupus erythematosus and antiphospholipid syndrome, and a history of pre-eclampsia. Moderate risk was defined as women with nulliparity, obesity with body mass index of 30 $kg/m^2$ or more, family history of pre-eclampsia, advanced maternal age of more than 35 years old, personal history factors such as small for gestational age or low birthweight, previous adverse pregnancy outcome, or more than

10-year pregnancy interval[2]. The authors did not use sociodemographic characteristics criteria because it was difficult to assess, and no clearly defined terms are available.

Exclusion criteria were patients with a history of kidney or ureteric stone, parathyroid disorders, untreated nasal polyp, aspirin-induced bronchospasm, gastrointestinal or urinary hemorrhage, severe liver disease, hypercalcemia, allergic to aspirin or $CaCO_3$, and other underlying diseases already receiving aspirin or calcium supplementation. Hypercalcemia was defined as having more than 10.5 mg/dL of serum corrected calcium level.

### Sample size calculation

The sample size estimation was calculated based on a previous study. The incidence of pre-eclampsia in the high-risk population treated with low-dose aspirin was 18%[13]. The expected reduction of incidence of pre-eclampsia was 70% among women treated with elemental calcium plus aspirin compared to aspirin alone[4]. A sample size of 202 participants, with 101 in each arm, would have 80% power to demonstrate whether high-dose $CaCO_3$ plus aspirin decreases the incidence of pre-eclampsia with severe features at a two-sided significance level of 5%. With an allowance of 10% for loss to follow-up, 222 participants were required, divided into 1:1 ratio, with 111 participants per group.

Because of the limited time frame and recruitment issue due to the COVID-19 situation, the authors had to analyze the data despite the insufficient number of participants.

### Randomization and masking

The participants were allocated and randomized on arrival at the clinic into two groups in a 1:1 ratio using a computer-generated randomization list with a random block size of four (Sealed Envelope™).

Calcium supplementation in the present study was 1,250 mg $CaCO_3$ tablet, with 40% of elemental calcium. Therefore, each 1,250 mg $CaCO_3$ tablet contains 500 mg of elemental calcium.

The intervention group received 81 mg/day of aspirin plus 3,750 mg/day of $CaCO_3$ divided into three times a day. The control group received 81 mg/day of aspirin plus 1,250 mg/day of $CaCO_3$. All participants received aspirin, and high-dose $CaCO_3$ for the intervention group, at 12 weeks of gestation or at the time of enrollment if they visited the antenatal clinic after 12 weeks of gestation. The patients were instructed to take aspirin until 36 weeks of gestation due to local hospital protocol or until the diagnosis of pre-eclampsia with severe features was achieved. In the intervention group, the patient took high-dose $CaCO_3$ until delivery or until they developed pre-eclampsia with severe features. Those screened prior to 12 weeks of gestation and eligible for the present trial were appointed to visit the clinic at 12 weeks of gestation to start low-dose aspirin and $CaCO_3$, according to the randomized arm. All the patients received other standard antenatal care, including other supplementation such as Obimin AZ, gestational diabetes mellitus screening, anomaly screening ultrasound, and vaccination as indicated for tetanus and influenza. Their prenatal care was scheduled by the standard local hospital guideline, which scheduled every four weeks until the 28 weeks of gestation, then every two weeks until the 36 weeks, and weekly after that until delivery. Weight and maternal vital signs, heart rate, and blood pressure were measured at each visit. If the blood pressure exceeded 140/90 mmHg, a blood test will be drawn for complete blood count (CBC), blood urea nitrogen (BUN), creatinine (Cr), aspartate aminotransferase (AST), alanine aminotransferase (ALT) urine protein-creatinine ratio (UPCR), and coagulogram. The outcome assessor and evaluator were blinded. The participants and the physician at the clinic were not blinded.

### Outcomes

Demographic data included age, underlying medical diseases, pre-pregnancy body weight, height, body mass index, smoking history, gestational age at enrollment, history of previous pregnancy such as term, preterm, and abortion, number of years since last-child delivery, amount of maternal milk consumption during pregnancy, treatment compliance, baseline calcium, and albumin level were recorded. Maternal milk consumption was assessed by asking the type, brand, and amount of milk intake, then multiplying the volume of milk by frequency of intake as times per day. The corrected serum total calcium level was calculated by adding the measured serum total calcium level to 0.8 mg/dL for every 1.0 g/dL of serum albumin below 4 mg/dL[14]. Hypocalcemia was defined as a corrected serum total calcium level of less than 8.4 mg/dL[15].

The primary outcome was the incidence of pre-eclampsia with severe features. The secondary outcomes were gestation age at delivery, route of delivery, and incidence of gestational hypertension or pre-eclampsia without severe features, incidence of HELLP (hemolysis, elevated liver enzymes, and

low platelets) syndrome, laboratory outcome (e.g., platelet, BUN, Cr, AST, ALT, lactate dehydrogenase [LDH], UPCR), maternal intensive care unit (ICU) admission, and length of stay, infant birthweight, Apgar score, neonatal intensive care unit (NICU), and sick newborn (SNB) admission and length of stay. If patients had more than one laboratory assessment, only the latest laboratory data before delivery was used. Side effects were assessed, including urolithiasis, gastrointestinal hemorrhage, postpartum hemorrhage, leg cramping, nausea and vomiting, constipation, and fetal seizure. According to the American Gastroenterological Association position statement, constipation was defined as having fewer than three bowel movements per week[16]. If the participant delivered at other hospitals, the authors would request the data from each hospital.

The primary outcome was defined using the criteria for diagnosing pre-eclampsia with severe features. Pre-eclampsia was defined as having systolic blood pressure (SBP) of 140 mmHg or higher or diastolic blood pressure (DBP) of 90 mmHg or higher on two occasions at least four hours apart after 20 weeks of gestation with evidence of proteinuria, such as 300 mg or more per 24 hours of urine collection, UPCR of 0.3 mg/dL or more, and dipstick reading of 2+. Pre-eclampsia with severe features was defined as having SBP of 160 mmHg or more or DBP of 90 mmHg or more or having other severe features such as thrombocytopenia with the platelet of less than $100{,}000\times10^3/\mu L$, impaired liver function with elevated AST or ALT twice the upper limit of normal concentration, severe persistent epigastric or right upper quadrant pain or unresponsive to medication, renal insufficiency with Cr greater than 1.1 mg/dL or doubling of the serum Cr concentration without other renal diseases, pulmonary edema, new-onset headache unresponsive to medication, and visual disturbances.

### Statistical analysis

Data were analyzed using the IBM SPSS Statistics, version 28.0 (IBM Corp., Armonk, NY, USA). All of the outcomes were calculated using intention-to-treat analysis. Categorial data were compared using Fisher's exact test and univariate logistic regression. Student's t-tests and linear regression were used in the normally distributed continuous variables to compare between groups. Non-normal distributed data were analyzed using the Mann-Whitney U test.

Results were expressed as means, standard deviation (SD), medians, range, and interquartile range (IQR) as appropriate. Odds ratios (ORs), mean differences, and 95% confidence intervals were used to calculate the effect size. A p-value less than 0.05 was considered statistically significant.

## Results

Two thousand one hundred ninety-three pregnant women were screened at the antenatal clinic. Among them, 72 women were identified with high risk and 58 with moderate risk of developing pre-eclampsia according to the ACOG guideline. They were randomized into two groups, the high-dose $CaCO_3$ group and the standard-dose $CaCO_3$ group. There were two cases with prescription errors in the intervention arm who received the standard-dose $CaCO_3$. There were four cases with loss of follow-up, three cases of spontaneous abortion, and one case with hydrocephalus, and received medical termination of pregnancy.

There was no significant difference in the clinical characteristic between the two randomized arms, including age, ethnicity, body weight, height, body mass index (BMI), smoking, gestational age at randomization, gravida, baseline corrected serum calcium level, and indication for starting aspirin (Table 1).

There were 15 cases (11.9%) of PIH in the intervention group and 14 cases (11.1%) in the control group, which was not statistically significant (p=0.833). The rate of pre-eclampsia with severe features was 1.7% lower in the intervention group at 4.9% versus 6.6%, respectively, which was not statistically different. Women receiving high-dose $CaCO_3$ had a non-significant difference in the incidence of gestational hypertension and pre-eclampsia without severe features. Gestational age at the diagnosis, maternal ICU admission, compliance, and laboratory results also no differences between the groups. None of the participants had eclampsia or HELLP syndrome (Table 2).

Most pregnancies in the present study population had normal corrected serum calcium levels. All participants' mean corrected serum calcium level was 9.3 mg/dL. There was only one case of hypo-calcemia. They mostly took at least one box of milk of 180 mL/day (Table 2), and the mean volume of milk consumption was 242.8 mL/day among all participants.

There was no statistically significant difference in neonatal outcomes (Table 3). No differences in adverse events, side effects, or complications were

**Table 1.** Clinical characteristic of study patients

| | High-dose $CaCO_3$ (n=64) | Standard dose $CaCO_3$ (n=66) | p-value |
|---|---|---|---|
| Age (year); mean±SD | 33.8±6.2 | 34.6±5.8 | 0.459 |
| Ethnicity; n (%) | | | 0.244 |
| Thai | 63 (98.4) | 62 (93.9) | |
| Myanmar | 0 (0.0) | 3 (4.6) | |
| Cambodia | 1 (1.6) | 1 (1.5) | |
| Pre-pregnancy body weight (kg); mean±SD | 73.8±2.3 | 71.8±2.2 | 0.528 |
| Height (cm); mean±SD | 157.8±6.5 | 157.2±5.4 | 0.609 |
| BMI ($kg/m^2$); mean±SD | 29.6±6.8 | 29.0±7.0 | 0.651 |
| Smoking; n (%) | 0 (0.0) | 0 (0.0) | - |
| Indication for aspirin; n (%) | | | |
| High risk | | | |
| • History of pre-eclampsia | 8 (12.5) | 6 (9.1) | 0.582 |
| • Multifetal gestation | 4 (6.3) | 5 (7.6) | 1.000 |
| • Chronic hypertension | 13 (20.3) | 18 (27.3) | 0.413 |
| • Diabetes | 11 (17.2) | 11 (16.7) | 1.000 |
| • Renal disease | 0 (0.0) | 0 (0.0) | - |
| • Autoimmune | 3 (4.7) | 2 (3.0) | 0.678 |
| Moderate risk | | | |
| • Nulliparity | 18 (28.1) | 21 (31.8) | 0.704 |
| • Obesity | 29 (45.3) | 32 (48.5) | 0.729 |
| • Family history of pre-eclampsia | 3 (4.7) | 1 (1.5) | 0.361 |
| • Age 35 years or older | 36 (56.3) | 41 (62.1) | 0.593 |
| • Personal history factors | 20 (31.3) | 26 (39.4) | 0.363 |
| GA at randomization (weeks); mean±SD | 17.6±5.2 | 18.8±4.6 | 0.187 |
| Gravida; means±SD | 2.2±1.1 | 2.4±1.2 | 0.395 |
| Corrected serum total calcium level (mg/dL); mean±SD | 9.3±0.4 | 9.3±0.4 | 0.742 |
| Hypocalcemia; n (%) | 1 (1.6) | 0 (0.0) | 0.492 |

SD=standard deviation; BMI=body mass index; GA=gestational age

attributed to the supplementation (Table 4).

## Discussion

The imbalance in prostacyclin and thromboxane A2 metabolism was hypothesized to be involved in the pathogenesis of pre-eclampsia. Low-dose aspirin blocks the formation of thromboxane A2 and is used to prevent the development of pre-eclampsia[17,18]. The mechanism of calcium in reducing pre-eclampsia is poorly understood. Available evidence supports the theory that calcium supplementation may fill a dietary gap in calcium intake, which modulate both placental vascularization and systemic vasomotor activity[3,19].

The current study examined the effect of high-dose $CaCO_3$ on the development of pre-eclampsia with severe features. The present study differs from WHO guidelines by using inclusion criteria as the criteria used for starting aspirin indicated by USPSTF[3,20]. Timing for intervention is also different. The present study starts the intervention as soon as 12 weeks of gestation together with aspirin as USPSTF, in WHO guidelines starts at 20 weeks[3]. The regimen also differs because the authors used high-dose $CaCO_3$ co-administrate with low-dose aspirin, which has not been reported before. Most trials evaluated the effect of high-dose calcium but not concurrently with aspirin. There is only one trial that uses both aspirin and high-dose calcium together. Bassaw et al. had made a 3-arm RCT compared 1,200 mg/day of elemental calcium versus 600 mg/day of elemental calcium plus aspirin versus 80 mg/day of aspirin. The present study used 1.5 g/day elemental calcium instead of 600 mg/day[4]. They found that aspirin plus 600 mg/day of elemental calcium could reduce the incidence of pre-eclampsia from 14.8% to 8% for control versus aspirin alone, and 2.4% for control versus calcium plus aspirin. The different results may be influenced by different inclusion criteria. They recruited primigravida and women with a history of pre-eclampsia. The baseline calcium diet may also

**Table 2.** Maternal Outcome

| | High-dose $CaCO_3$ (n=64) | Standard dose $CaCO_3$ (n=66) | Effect size (95% CI) | p-value |
|---|---|---|---|---|
| Route of delivery; n (%) | | | OR 0.7 (0.3 to 1.5) | 0.450 |
| Vaginal delivery | 23 (35.9) | 21 (31.8) | | |
| Cesarean delivery | 34 (53.1) | 44 (66.7) | | |
| GA at delivery (weeks); mean±SD | 37.6±2.6 | 37.2±2.8 | MD 0.4 (–0.6;1.4) | 0.438 |
| Pregnancy induced hypertension | | | | |
| Gestational hypertension; n (%) | 5 (7.8) | 4 (6.1) | OR 1.5 (0.4 to 5.8) | 0.732 |
| • GA at diagnosis (weeks); means±SD | 36.7±3.6 | 35.7±1.1 | MD 0.01 (–4.5;4.5) | 0.620 |
| Pre-eclampsia without SF; n (%) | 8 (12.5) | 4 (6.1) | OR 2.5 (0.7 to 8.8) | 0.223 |
| • GA at diagnosis (weeks); mean±SD | 34.0±5.5 | 34.5±3.3 | MD 1.0 (–5.1;7.2) | 0.859 |
| • Superimposed from CHT; n (%) | 2 (3.1) | 3 (4.6) | OR 0.7 (0.1 to 4.3) | 1.000 |
| Pre-eclampsia with SF; n (%) | 6 (9.4) | 8 (12.1) | OR 0.8 (0.3 to 2.6) | 0.785 |
| • GA at diagnosis (weeks); mean±SD | 36.5±3.2 | 33.9±3.6 | MD 1.1 (–3.2;5.4) | 0.185 |
| • Superimposed from CHT; n (%) | 1 (1.6) | 7 (10.6) | OR 0.1 (0.02 to 1.16) | 0.063 |
| HELLP syndrome; n (%) | 0 (0.0) | 0 (0.0) | - | - |
| Maternal ICU admission; n (%) | 0 (0.0) | 1 (1.5) | - | 1.000 |
| Maternal death; n (%) | 0 (0.0) | 0 (0.0) | - | - |
| Milk consumption (mL); mean±SD | 253.5±170.4 | 233.4±115.1 | MD 20.1 (–31.5;71.7) | 0.442 |
| Compliance (%); mean±SD | 91.8±15.6 | 92.8±16.5 | MD –1.0 (–6.8;4.8) | 0.737 |
| Laboratory results; mean±SD | | | | |
| Hemoglobin (g/dL) | 37.6±2.6 | 37.2±2.8 | MD –0.4 (–0.9;0.2) | 0.193 |
| Platelet ($10^6$/μL) | 269.8±69.4 | 266.2±81.6 | MD 3.6 (–29.2;36.4) | 0.414 |
| BUN (mg/dL) | 10.9±4.1 | 10.0±5.3 | MD 0.9 (–2.2;4.0) | 0.545 |
| Creatinine (mg/dL) | 0.7±0.2 | 0.7±0.2 | MD 0.03 (–0.1;0.2) | 0.660 |
| AST (unit/L) | 31.4±33.9 | 47.0±65.0 | MD –15.6 (–49.3;18.1) | 0.355 |
| ALT (unit/L) | 32.6±67.5 | 61.9±143.2 | MD –29.3 (–102.3;43.6) | 0.421 |
| LDH (unit/L) | 218.1±44.7 | 252.7±63.6 | MD –34.5 (–100.8;31.8) | 0.276 |
| UPCR | 1.1±2.6 | 1.4±2.9 | MD –0.4 (–2.1;1.4) | 0.679 |
| INR | 0.99±0.06 | 0.98±0.05 | MD 0.01 (–0.02;0.05) | 0.438 |

MD=mean difference; OR=odd ratio; CI=confidence interval; SD=standard deviation; GA=gestational age; CHT=chronic hypertension; SF=severe features; $CaCO_3$=calcium carbonate; HELLP=hemolysis, elevated liver enzymes and low platelets; ICU=intensive care unit; BUN=blood urea nitrogen; AST=aspartate aminotransferase; ALT=alanine aminotransferase; LDH=lactate dehydrogenase, UPCR=urine protein, creatinine ratio; INR=international normalized ratio

**Table 3.** Neonatal outcomes

| | High-dose $CaCO_3$ (n=64) | Standard dose $CaCO_3$ (n=66) | p-value |
|---|---|---|---|
| Birthweight (g); mean±SD | 3015.1±747.6 | 2,829.5±842.5 | 0.190 |
| Apgar; median (IQR) | | | |
| 1 minute | 9 (8 to 9) | 9 (8 to 9) | 0.467 |
| 5 minutes | 10 (9 to 10) | 10 (9 to 10) | 0.823 |
| Apgar score ≤7 at 1-minute; n (%) | 5 (7.8) | 6 (9.1) | 1.000 |
| Apgar score ≤7 at 5-minute; n (%) | 3 (4.7) | 4 (6.1) | 1.000 |
| NICU admission; n (%) | 4 (6.3) | 8 (12.1) | 0.383 |
| NICU length of stay; median (range) | 0 (51) | 0 (168) | 0.445 |
| SNB admission; n (%) | 20 (31.3) | 18 (27.3) | 0.439 |
| SNB length of stay; median (range) | 0 (63) | 0 (38) | 0.473 |
| Neonatal death; n (%) | 3 (4.7) | 0 (0.0) | 0.096 |

$CaCO_3$=calcium carbonate; SD=standard deviation; IQR=interquartile range; NICU=neonatal intensive care unit; SNB=sick newborn

be different, which was not mentioned.

High-dose $CaCO_3$ supplementation did not alter neonatal outcomes and can be used safely during pregnancy. High-dose $CaCO_3$ also did not increase

**Table 4.** Adverse events

| | High-dose $CaCO_3$ (n=64) | Standard dose $CaCO_3$ (n=66) | p-value |
|---|---|---|---|
| Abortion; n (%) | 4 (6.3) | 0 (0.0) | 0.052 |
| Urolithiasis; n (%) | 0 (0.0) | 0 (0.0) | - |
| Gastrointestinal bleeding; n (%) | 0 (0.0) | 0 (0.0) | - |
| PPH; n (%) | 0 (0.0) | 1 (0.8) | 1.000 |
| Constipation; n (%) | 1 (1.6) | 3 (4.6) | 0.622 |
| Leg cramping (times/week); median (IQR) | 0.3 (0 to 1) | 0.0 (0 to 1) | 0.156 |
| N/V (times/week); median (range) | 0.0 (7) | 0.0 (21) | 0.216 |

$CaCO_3$=calcium carbonate; SD=standard deviation; PPH=postpartum hemorrhage; IQR=interquartile range; N/V=nausea and vomiting

the incidence of common side effects of $CaCO_3$ such as constipation, leg cramping, nausea, and vomiting. This may have contributed to the high calcium diet in the studied population.

The strength of the present study is that this is a pragmatic trial in which participants were recruited using specific criteria and the timing was the same as the ACOG used for starting aspirin. The authors also demonstrated the amount of calcium diet, which was not mentioned in the previous study. The authors did not interfere with the patient's diet. So, it reflects the actual effect of high-dose calcium on the population.

The major limitation of the present study is the insufficient number of patients. The authors could not achieve the target numbers due to the COVID-19 situation caused the patients to visit the local antenatal clinic instead of the hospital. Further, the dose of aspirin used in the present study differed from the ASPRE trial, which uses 150 mg/day of aspirin[21]. The present study used 81 mg/day of aspirin due to local guidelines based on ACOG recommendations[2].

The population in the present study had a normal baseline serum corrected calcium level. Moreover, they also took milk as an extra calcium supplement. The means extra milk consumption was 242.8±143.3 mL/day. A box of milk drank by most women in the present study had 600 mg of calcium in each 180 mL box. Therefore, the mean total extra calcium consumption was 809.3±477.6 mg/day. All pregnant women received 1,250 mg/day of $CaCO_3$ as a standard supplementation. Consequently, they received approximately at least 1,300 mg/day of elemental calcium, excluding other calcium-contained diets, almost as high as receiving high-dose elemental calcium according to the WHO guidelines. The effect of calcium supplementation may be decreased because of an extra calcium diet.

To enhance the result of the present study, future research may be required to demonstrate the actual effect of high-dose $CaCO_3$. The authors suggest that future studies may be improved by increasing the number of participants, using a higher dose of aspirin at 150 mg/day, and decrease the confounding factor from the milk consumption.

## Conclusion

The use of $CaCO_3$ at 3,750 mg/day co-administrate with low-dose aspirin of 81 mg/day, starting at 12 to 28 weeks of gestation, resulted in a non-significant difference in the incidence of pre-eclampsia with severe features. A high milk intake as an extra calcium supplementation might be substituted for high-dose $CaCO_3$ supplementation. The interpretation of the findings is limited by its underpower. The authors believe that the present study findings should be further investigated, and the effect of a high calcium diet on PIH prevention should be investigated.

## What is already known on this topic?

High-dose calcium supplementation is effective in reducing the incidence of pre-eclampsia in high-risk population with low calcium diet. But the optimal doses and timing are not known. The high-risk of developing pre-eclampsia were define in WHO guidelines is different from ACOG guidelines.

## What this study adds?

This study reveals the effect of high-dose $CaCO_3$ in a large city in the eastern part of Thailand. The incidence of pre-eclampsia did not reduce in the high-dose $CaCO_3$ groups. The amount of milk intake is high in this population, which may contribute to the lower effect of $CaCO_3$. The high-dose $CaCO_3$ is not necessary for this population because they have a high intake of calcium.

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## Conflicts of interest

The authors declare no conflict of interest.

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